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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/747,165	12/22/2000	Richard W. Tseng	034827-0302	1234

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/747,165	TSENG ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *26 June 2002* .

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-6 and 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mensink et al (British J. Haematol. (August 1998) 102:768-774) in view of Hariharan et al (EMBO J. 6(1):115-119 (1987)) and further in view of Shtivelman (Cell 47:277-284 (1986)) and further in view of Buck et al (Biotechniques (1999) 27(3):528-536).

Mensink teaches a method for determining bcr-abl translocation rearrangements for the diagnosis of CML (abstract) comprising the steps of:

a) extracting RNA from a biological sample (page 769, subheading "RNA isolation and cDNA synthesis") and including RNAsin RNAse inhibitor (page 769, column 2),

b) quantifying the extracted RNA by use of PBGD expression (page 770, column 1),

c) reverse transcribing the RNA to cDNA (page 769, column 2),

d) amplifying the cDNA and detecting a cDNA signal using BCR-ABL probes and primers (page 769, column 2),

e) obtaining a standard curve of cDNA signals from serial dilutions of a leukemic cell line, wherein the cDNA is obtained by repeating steps a)-d) with the RNA from the leukemic cell line and not the sample (page 770, subheading "quantitation")

f) extrapolating a measurement of the leukemic cells present in the sample by comparing the signal from step d) with that from step e) (page 770, subheading "quantitation" and page 771, figure 1)

Mensink teaches what he terms "Real Time" detection for steps d) and e) (page 769, column 2).

Mensink teaches that less than a certain amount of BCR-ABL is designated as below detection level and above a certain level is positive (page 770, column 1 last sentence to column 2, first sentence). Mensink teaches that the detection limit is 1 in ten thousand cells (page 770, column 2).

Mensink teaches the normalized dose as a measurement of leukemic cells present in the sample (page 771, table I).

Mensink teaches amplification and detection of the cDNA in a single container (page 769, column 2, subheading "Real Time quantitation using Taqman assay").

Mensink does not teach one of the particular oligonucleotides of SEQ ID NO:s 1-8, but Mensink does teach primer selection "Using the Primer Express software program (Perkin-Elmer, Foster City, Calif. Demo version 1.0 ppd) we designed PCR primers for the amplification of cDNA derived from the BCR-ABL transcript and PBGD transcript (page 769, column 2)".

Hariharan teaches the cDNA sequence for BCR (page 117, figure 2). See alignment below.

```
Human mRNA for bcr (breakpoint cluster region) gene in Philadelphia
           chromosome
         Length = 4739

 Score = 38.2 bits (19), Expect = 0.015
 Identities = 19/19 (100%)
 Strand = Plus / Plus


Query: 1    cctcgcagaactcgcaaca 19
             ||||||||||||||||||
Sbjct: 1597 cctcgcagaactcgcaaca 1615


Human mRNA for bcr (breakpoint cluster region) gene in Philadelphia
           chromosome
         Length = 4739

 Score = 40.1 bits (20), Expect = 0.012
```

```
 Identities = 20/20 (100%)
 Strand = Plus / Plus


Query: 1    gagctgcagatgctgaccaa 20
             ||||||||||||||||||||
Sbjct: 3120 gagctgcagatgctgaccaa 3139
```

Shtivelman teaches the cDNA sequence for ABL (page 278, figures 1 and 2), see alignment below.

```
Human c-abl gene, complete cds
          Length = 3840

 Score = 44.1 bits (22), Expect = 0.001
 Identities = 22/22 (100%)
 Strand = Plus / Minus


Query: 1    tcagaccctgaggctcaaagtc 22
             ||||||||||||||||||||||
Sbjct: 491 tcagaccctgaggctcaaagtc 470
```

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Mensink with the use of functionally equivalent primers selected from the sequences of Hariharan and Shtivelman since Mensink expressly teaches primer selection using commercially available software for BCR-ABL detection from the BCR-ABL published sequences and since Hariharan and Shtivelman provide such published sequences for the software program to analyze.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of BCR-ABL, and in particular for diagnosis of Chronic Myelogenous Leukemia, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly

striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

4. Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eder et al (Leukemia (September 1999) 13:1383-1389) in view of Hariharan et al (EMBO J. 6(1):115-119 (1987)) and further in view of Shtivelman (Cell 47:277-284 (1986)) and further in view of Ercolani et al (Journal of Biological Chemistry (1988) 263(30):15335-15341) and further in view of Buck et al (Biotechniques (1999) 27(3):528-536).

Eder teaches a method for determining bcr-abl translocation rearrangements for the diagnosis of CML (abstract) comprising the steps of:

a) extracting RNA from a biological sample (page 1384, column 1, subheading "RNA isolation")

b) quantifying the extracted RNA by use of GAPDH expression (page 1384, column 2),

c) reverse transcribing the RNA to cDNA (page 1384, column 1),

d) amplifying the cDNA and detecting a cDNA signal using BCR-ABL probes and primers and GAPDH probes and primers (page 1384, subheading "Realtime PCR"),

e) obtaining a standard curve of cDNA signals from serial dilutions of a leukemic cell line, wherein the cDNA is obtained by repeating steps a)-d) with the RNA from the leukemic cell line such as K562 and not the sample (page 1384, column 2, subheading "normalization and quantitation")

f) extrapolating a measurement of the leukemic cells present in the sample by comparing the signal from step d) with that from step e) (page 1384, column 2 and page 1385, fugre 1).

Eder teaches what he terms "Real Time" detection for steps d) and e) (page 1384, column 1).

Eder teaches the use of the Trizol reagent, which inhibits RNAse activity (page 384, column 1).

Eder runs the cDNA products on an electrophoretic gel to obtain fragment size and identity information (page 1385, figure 1).

Eder teaches that less than a certain amount of BCR-ABL is designated as below detection level and above a certain level is positive (page 1384, column 2). Eder teaches that the detection limit is 1 in ten thousand cells (page 1385, figure 1).

Eder teaches the normalized dose as a measurement of leukemic cells present in the sample (page 1385, table I).

Eder teaches amplification and detection of the cDNA in a single container (page 1384, column 1, subheading "Real Time PCR").

Eder does not teach one of the particular oligonucleotides of SEQ ID NO:s 1-8, but Eder does teach primer selection "Using the Primer Express software version 1.0 (Perkin-Elmer/Applied Biosystems, Foster City, USA) (page 1384, column 1)."

Hariharan teaches the cDNA sequence for BCR (page 117, figure 2). See alignment below.

```
Human mRNA for bcr (breakpoint cluster region) gene in Philadelphia
          chromosome
        Length = 4739
```

```
 Score = 38.2 bits (19), Expect = 0.015
 Identities = 19/19 (100%)
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Query: 1    cctcgcagaactcgcaaca 19
             ||||||||||||||||||
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Human mRNA for bcr (breakpoint cluster region) gene in Philadelphia
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 Identities = 20/20 (100%)
 Strand = Plus / Plus


Query: 1    gagctgcagatgctgaccaa 20
             ||||||||||||||||||||
Sbjct: 3120 gagctgcagatgctgaccaa 3139
```

Shtivelman teaches the cDNA sequence for ABL (page 278, figures 1 and 2), see alignment below.

```
Human c-abl gene, complete cds
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 Identities = 22/22 (100%)
 Strand = Plus / Minus


Query: 1    tcagaccctgaggctcaaagtc 22
             ||||||||||||||||||||||
Sbjct: 491 tcagaccctgaggctcaaagtc 470
```

Ercolan teaches the DNA sequence for GAPDH (page 15340, figure 2) see alignment below.

```
Human glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene, complete
           cds
          Length = 5378

 Score = 40.1 bits (20), Expect = 0.012
```

```
 Identities = 20/20 (100%)
 Strand = Plus / Minus


Query: 1    gaagatggtgatgggatttc 20
             ||||||||||||||||||||
Sbjct: 3407 gaagatggtgatgggatttc 3388
```

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Eder with the use of functionally equivalent primers selected from the sequences of Hariharan, Shtivelman and Ercolani since Eder expressly teaches primer selection using commercially available software for BCR-ABL detection from the BCR-ABL published sequences and since Hariharan, Shtivelman and Ercolani provide such published sequences for the software program to analyze.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of BCR-ABL and GAPDH, and in particular for diagnosis of Chronic Myelogenous Leukemia, and concerning which a biochemist of ordinary skill would

attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Response to Arguments

5. Applicant's arguments filed June 12, 2003 have been fully considered but they are not persuasive.

The examiner notes that the 112, second paragraph rejection is withdrawn.

Applicant argues with regard to the 103 rejection that there is no expectation of function. It is noted that Applicant's invention, to the extent that there is any novelty, relies solely on the selection of particular primers. The prior art of both Mensink and Eder teach performance of real time PCR to detect the BCR-abl translocation, just as desired by Applicant. Further, the sequence from which the primers were derived is taught by Shtivelman and Hariharan. Finally, Mensink teaches the primer express software that is used to select the desired primers with all of the required parameters. Consequently, selection of specific primers is prima facie obvious since selection of equivalent primers to those of Mensink, using the software of Mensink, is prima facie obvious.

Applicant requested objective evidence that selection of primers would result in equivalent function. As noted in the rejection, the Buck reference provides such evidence. Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence

that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Applicant cites the He et al reference to argue that primers are not equivalent. He et al is not sufficient to rebut Buck for several reasons. First, Buck is a 1999 paper which actually tested about 164 primers selected both to cover the entire region of interest at random and by the methods of 39 different labs and Buck found that all of these 164 primers functioned in the sequencing assay. He is a much older 1994 paper which is focused on a particular sensitivity. He does not show that any of the primer pairs do not work, but simply shows that there is variation in efficiency. This showing does not rebut the argument that primers are equivalent, but simply shows that unexpected results are possible. Applicant cites other references that primer design software should be regarded skeptically. In fact, as Buck shows, any form of design functions to yield effective primers. None of the references cited by Applicant actually experimentally tested their concerns. Therefore, Buck's empirical test that all 164 primers chosen functioned is more persuasive regarding the equivalence of primers than the untested opinions of others. Currently, there is no evidence submitted by Applicant which shows any sort of unexpected results for the claimed primers.

Finally, Applicant argues that the multiplex nature of the assay is unexpected. Mensink expressly teaches a multiplex assay to detect each of these variants as he

notes "This enabled detection and quantitation of the most common 82A2 and B3A2 fusion transcript. To also detect the B1A2 splicing variant one additional B1 primer should be included. (see page 773, column 1)". Thus, the multiplex nature of the assay is not at all unexpected, but in fact, is the desired and expected method. Thus, there is an express teaching and suggestion to multiplex, contrary to Applicant's assertion.

Therefore the rejections are maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634

July 25, 2003